

Epidemiology and the Risk Factors for Mortality in Ventilator-Associated Pneumonia

Ventilatör ile İlişkili Pnömonide Epidemiyoloji ve Mortalite ile İlişkili Risk Faktörleri

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ABSTRACT

Objective: Ventilator-associated pneumonia (VAP) is the most common hospital-acquired infections in intensive care units (ICUs) and associated with prolonged hospital stay, increased mortality and cost. This study aims to analyse the epidemiology and the risk factors affecting 30 day-mortality in VAP.

Method: Adult patients with VAP were included in the study. Data were obtained from infection control committee records. Patients were followed up for mortality until 30 days after onset of VAP or until death for the patients died within 30 days. Survivor and non-survivor groups were compared as for the predictors of mortality.

Results: A total of 183 VAP patients were evaluated. Early-onset VAP was observed in 16 (8.7%), and late-onset VAP in 167 (91.3%) patients. *Acinetobacter baumannii* was the most common cause of VAP (49.2%), followed by *Pseudomonas aeruginosa* (19.7%) and *Klebsiella pneumoniae* (13.7%). Carbapenem resistance was seen in 78 (42.6%) patients and among them, most frequently *Acinetobacter baumannii* (62.8%, 49/78), followed by *Klebsiella pneumoniae* (20.5%, 16/78), *Pseudomonas aeruginosa* (14.1%, 11/78) and *Escherichia coli* (2.6%, 2/78) were isolated. Thirty day-mortality rate was 46.4% (n=85). In univariate analysis; malignity, blood transfusion, renal replacement therapy, Higher APACHE II, SOFA and SAPS 2 scores on the day of VAP onset and *Acinetobacter baumannii* were found to be more common in non-survivor group. According to the Cox-regression analysis, only SOFA score on the day of VAP onset and *Acinetobacter baumannii* were independent predictors of mortality. Although rate of trauma patients was significantly higher in survivor group, in multivariate analysis it was not a protective factor for mortality.

Conclusion: The most common cause of VAP was *Acinetobacter baumannii* and carbapenem resistance was seen in more than half of *Acinetobacter baumannii* and *Klebsiella pneumoniae* isolates. Higher SOFA score on the day of VAP onset and *Acinetobacter baumannii* infections were found to be independently associated with 30-day mortality in VAP patients.

Keywords: ventilator-associated pneumonia, mortality, SOFA score, *Acinetobacter baumannii*

Öz

Amaç: Ventilatörle ilişkili pnömoni (VIP), yoğun bakım üniteleri (YBÜ)'de en sık hastane kaynaklı enfeksiyonlardan biridir ve uzun süreli hasta- ne yatışı, artan ölüm oranı ve maliyet ile ilişkilidir. Bu çalışma, YBÜ'de VIP tanılı hastalarda epidemiyoloji ve 30 günlük mortaliteyi etkileyen risk faktörlerini irdelemeyi amaçlamaktadır.

Yöntem: Erişkin VIP hastaları çalışmaya dahil edildi. Hasta verileri enfeksiyon kontrol komitesi kayıtlarından elde edildi. Hastalar VIP başlan- gıcından 30 gün sonrasına kadar veya 30 gün içinde öldüyse ölene kadar mortalite açısından takip edildi. Yaşayan ve ölen hastalar risk faktö- reri açısından karşılaştırıldı.

Bulgular: Çalışmaya toplam 183 VIP hastası dahil edildi. Erken başlangıçlı VIP 16 (%8,7) hastada, geç başlangıçlı VIP 167 (%91,3) hastada görüldü. En sık VIP etkeni *Acinetobacter baumannii* idi (%49,2), bunu *Pseudomonas aeruginosa* (%19,7) ve *Klebsiella pneumoniae* (%13,7) izledi. 78 (%42,6) hastada karbapenem direnç görüldü. Bu hastalarda sıklık sırasına göre *Acinetobacter baumannii* (%62,8, 49/78), *Klebsiella pneumoniae* (%20,5, 16/78), *Pseudomonas aeruginosa* (%14,1, 11/78) ve *Escherichia coli* (%2,6, 2/78) izole edildi. Çalışmada otuz günlük mortalite oranı %46,4 (n=85) olarak bulundu. Tek değişkenli analizde; ölen grupta malignite, kan transfüzyonu, renal replasman tedavisi, APACHE II, SOFA ve SAPS II skorları ve *Acinetobacter baumannii* sıklığının daha fazla olduğu görüldü. Cox-regresyon analizine göre, sadece VIP geliştiği andaki SOFA skoru ve *Acinetobacter baumannii* mortalitenin için bağımsız risk faktörü olarak bulundu. Yaşayan grupta travma has- talarının oranı anlamlı olarak daha yüksek olmasına rağmen, travma çok değişkenli analizde mortalite için koruyucu bir faktör değildi.

Sonuç: VIP hastalarında en sık etken *Acinetobacter baumannii* idi ve karbapenem direnci *Acinetobacter baumannii* ve *Klebsiella pneumoniae* izolatlarının yarısından fazlasında görüldü. VIP geliştiği andaki SOFA skoru yüksekliği ve *Acinetobacter baumannii* enfeksiyonu VIP hastalarında 30 günlük mortalite ile bağımsız olarak ilişkili bulundu.

Anahtar kelimeler: ventilatörle ilişkili pnömoni, mortalite, SOFA skoru, *Acinetobacter baumannii*

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is defined as the pneumonia developed more than 48 hours after intubation in patients on mechanical ventilation. It is one of the most common hospital-acquired infections in intensive care units (ICUs) and associated with prolonged duration of hospital stay, increased mortality rate and cost⁽¹⁻⁴⁾.

VAP develops in approximately 10–40% of patients on mechanical ventilation, with large variations among ICUs. Mortality rates due to VAP has been reported varying from 20% to 50% in the literature⁽⁵⁻⁸⁾. Prior studies have identified the risk factors that affect the prognosis of VAP⁽⁹⁻¹¹⁾. Multidrug-resistant (MDR) microorganisms, the severity of illness, and inadequate initial antibiotic therapy have been identified as determinants of ICU mortality in patients with VAP. Underlying diseases such as chronic obstructive pulmonary disease (COPD) are also believed to effect the mortality in VAP patients⁽¹²⁾. This study aims to analyse the epidemiology of VAP and identify the risk factors affecting 30 day-mortality of the patients with VAP in a tertiary care hospital ICU.

MATERIALS and METHODS

This retrospective study was conducted in a 612-bed tertiary care hospital which has a 31-bed Anesthesiology and Reanimation ICU, nine-bed neurology ICU, 16-bed coronary ICU, seven-bed cardiovascular ICU, 26-bed neonatal ICU and a 16-bed pediatric ICU. We performed the study in Anesthesiology and Reanimation ICU which accepts patients from both medical and surgical wards. The study was approved by the Ethics Committee.

Adult patients with VAP (≥ 18 years) who were hospitalized in ICU between January 2016 and January 2019 were included in the study. VAP is defined as a new or progressive pulmonary infiltration occurring more than 48 h after intubation in combination with at least 2 of the following criteria: temperature $>38.5^{\circ}\text{C}$ or $<36.5^{\circ}\text{C}$; change in character of sputum (purulent or increased amount of sputum); white blood cell count >10000 cells/ mm^3 or <4000 cells/ mm^3 ⁽¹³⁾. VAP is classified as early-onset VAP, occurring within 4 days of intubation, and late-onset VAP,

occurring on the fifth day or later, after intubation. Respiratory samples were obtained from either endotracheal aspirate (ETA) or bronchoalveolar lavage (BAL) to determine the causative microorganism and quantitative culture cut-off points of $>10^6$ CFU/ml and $>10^4$ CFU/ml were used respectively. In cases with recurrent VAP, only the first episode was included in the study. The patients who had pneumonia at admission, multiple microorganisms in the ETA culture or the patients who did not meet the VAP criteria despite the growth of microorganisms in the ETA culture were excluded from the study. Data about demographic characteristics, underlying diseases, length of ICU stay, invasive procedures, duration of mechanical ventilation prior to VAP, and causative microorganisms were retrieved from the infection control committee records. Acute Physiology and Chronic Health Evaluation (APACHE) II score, Sequential Organ Failure Assessment (SOFA) score and Simplified Acute Physiology Score (SAPS II) were recorded both on the admission day and the day of VAP onset. Patients were followed up for mortality until 30 days after onset of VAP or until death for the patients died within 30 days. Statistical analyses were performed by using the Statistical package for Social Sciences version 25.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive data were presented as mean \pm standard deviation, frequency, median and percentage values. Categorical variables were compared using chi-square test and Fisher's Exact test. The normality of continuous variables was tested with the Kolmogorov-Smirnov test. Student's t-test was used for comparing the normally distributed continuous variables and, Mann-Whitney U test for comparing the continuous variables which were not normally distributed. Cox regression analysis was used for multivariate analysis to evaluate the independent variables associated with 30-day mortality. The "p" values less than or equal to 0.05 ($p \leq 0.05$) were considered as statistically significant.

RESULTS

A total of 183 VAP patients were enrolled in the study. Out of them, 116 (63.4%) were male and 67 (36.6%) were female with an overall mean age of 53.15 ± 20.88 years (min: 18, max: 94). Early-onset VAP was observed in 16 (8.7%) patients and late-onset VAP in 167 (91.3%) patients. *Acinetobacter*

Table 1. Mortality associated risk factors in ventilator-associated pneumonia.

	Survivor (n=98)	Non-survivor (n=85)	p	OR	95% CI
Sex, n (%)					
Male	67 (68.4)	49 (57.6)			
Female	31 (31.6)	36 (42.4)	0.13	1.63	0.34-1.15
Age, year (mean±sd)	50.62±21.03	56.14±20.42	0.08		
Hospitalization before ICU, n (%)	40 (40.8)	40 (47.1)	0.39	1.28	0.71-2.31
Length of ICU stay, day, median (IQR)	32 (21-47)	31 (21-48)	0.85		
APACHE II on admission, median (IQR)	20 (15-25)	20 (15-26)	0.18		
SOFA on admission, median (IQR)	8 (5-10)	9 (6-11)	0.06		
SAPS II on admission, median (IQR)	45 (36-23)	48 (37-61)	0.16		
APACHE II on the day of VAP onset, median (IQR)	18 (12-23)	24 (19-28)	<0.001*		
SOFA on the day of VAP onset, median (IQR)	4 (3-7)	10 (6-3)	<0.001*		
SAPS II on the day of VAP onset, median (IQR)	39 (31-49)	48 (43-60)	<0.001*		
Duration of mechanical ventilation before VAP, day, median (IQR)	11 (7-19)	11 (7-18)	0.94		
Type of VAP, n (%)					
Early	7 (7.1)	9 (10.6)			
Late	91 (92.9)	76 (89.4)	0.41	0.65	0.23-1.82
Trauma, n (%)	34 (34.7)	15 (17.6)	0.009*	0.40	0.20-0.80
Secondary BSI, n (%)	2 (2)	5 (5.9)	0.17	3	0.56-15.88
Carbapenem resistance, n (%)	36 (36.7)	42 (49.4)	0.08	1.68	0.93-3.03
Colistin resistance, n (%)	1 (1)	3 (3.5)	0.33	3.5	0.36-34.77
Underlying diseases, n (%)					
Hypertention	24 (24.5)	25 (29.4)	0.45	1.28	0.66-2.47
Heart failure	6 (6.1)	9 (10.6)	0.27	1.81	0.61-5.33
Diabetes mellitus	13 (13.3)	14 (16.5)	0.54	1.28	0.56-2.92
Chronic renal failure	9 (9.2)	14 (16.5)	0.13	1.95	0.79-4.76
Coronary artery disease	11 (11.2)	7 (8.2)	0.49	0.71	0.26-1.92
Malignity	3 (3.1)	13 (15.3)	0.003*	5.71	1.57-20.81
COPD	8 (8.2)	5 (5.9)	0.54	0.70	0.22-2.23
Neurological diseases	7 (7.1)	4 (4.7)	0.48	0.64	0.18-2.27
Invasive procedures, n (%)					
Tracheostomy	75 (76.5)	60 (70.6)	0.36	0.73	0.38-1.42
Blood transfusion	74 (75.5)	78 (91.8)	0.003*	3.61	1.46-8.88
CVC	82 (83.7)	75 (88.2)	0.37	1.46	0.89-2.94
Nazogastric tube	97 (99)	85 (100)	1	1.87	1.63-2.15
Total parenteral nutrition	52 (53.1)	55 (64.7)	0.11	1.62	0.89-2.94
Hemodialysis/CRRT	26 (26.5)	51 (60)	<0.001*	4.1	2.22-7.75
Microorganism, n (%)					
<i>Klebsiella pneumoniae</i>	11 (11.2)	13 (15.3)	0.41	1.42	0.60-3.38
<i>Acinetobacter baumannii</i>	38 (38.8)	52 (61.2)	0.003*	2.48	1.37-4.51
<i>Pseudomonas aeruginosa</i>	24 (24.5)	12 (14.1)	0.07	0.5	0.23-1.08
<i>Staphylococcus aureus</i>	7 (7.1)	3 (3.5)	0.28	0.47	0.11-1.9

OR: Odd's ratio, sd: standard deviation, IQR: interquartile range VAP: ventilator-associated pneumonia, BSI: Bloodstream infection, CVC: Central venous catheter CRRT: continuous renal replacement therapy

baumannii was the leading cause of VAP (49.2%), followed by *Pseudomonas aeruginosa* (19.7%) and *Klebsiella pneumoniae* (13.7%). The distribution of microorganisms that caused VAP was shown in Figure 1. Carbapenem resistance was seen in 78 (42.6%) patients and among them, *Acinetobacter baumannii* (62.8%, 49/78), *Klebsiella pneumoniae* (20.5%, 16/78), *Pseudomonas aeruginosa* (14.1%, 11/78) and *Escherichia coli* (2.6%, 2/78) were isolated. The carbapenem resistance rates for each micro-

organism was shown in Figure 2. Colistin resistance was seen only in *Klebsiella pneumoniae* species in 4 (2.2%) patients. Secondary bloodstream infections were seen in seven patients, four of them were infected with *Acinetobacter baumannii*, two of them with *Klebsiella pneumoniae* and one of them with *S.aureus*.

Thirty day-mortality rate was found to be 46.4% (n=85) in the study. Survivor and non-survivor groups

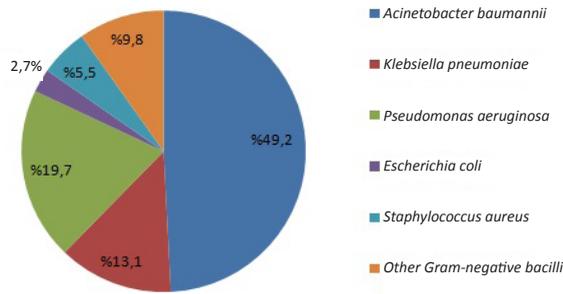


Figure 1. Distribution of bacteria that caused ventilator-associated VAP

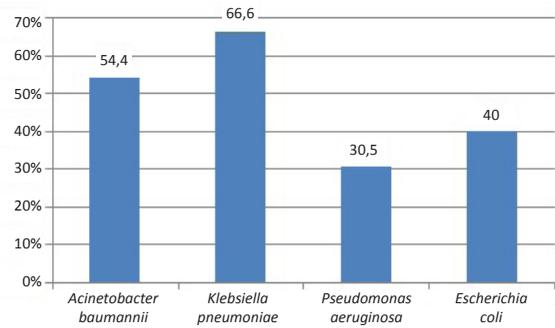


Figure 2. Carbapenem resistance rates for each bacteria.

Table 2. Cox regression analysis of risk factors for mortality in ventilator-associated pneumonia.

	Survivor (n=98)	Non-survivor (n=85)	p	OR	%95 CI
APACHE II on the day of VAP onset, median (IQR)	18 (12-23)	24 (19-28)	0.11	1.03	0.99-1.07
SOFA on the day of VAP onset, median (IQR)	4 (3-7)	10 (6-3)	0.03*	1.07	1-1.14
SAPS II on the day of VAP onset, median (IQR)	39 (31-49)	48 (43-60)	0.80	0.99	0.97-1.02
Trauma, n (%)	34 (34.7)	15 (17.6)	0.36	0.74	0.39-1.40
Malignity, n (%)	3 (3.1)	13 (15.3)	0.11	1.73	0.88-3.39
Blood transfusion, n (%)	74 (75.5)	78 (91.8)	0.11	2.10	0.83-5.33
Hemodialysis/CRRT, n (%)	26 (26.5)	51 (60)	0.2	0.7	0.4-1.21
<i>Acinetobacter baumannii</i> , n (%)	38 (38.8)	52 (61.2)	0.01*	1.82	1.12-2.96

were compared to determine the predictors of mortality. Demographic characteristics including age and sex, APACHE II, SOFA and SAPS II scores at ICU admission, length of ICU stay, the median duration of mechanical ventilation prior to VAP onset were not statistically different between two groups. The proportion of patients with early and late-onset VAP were similar in both survivor and non-survivor groups (p=0.41). Among underlying diseases, the history of malignity was found to be at significantly higher rates in non-survivor group (p=0.003, OR:5.71, 95% CI:1.57-20.81). In terms of invasive procedures in ICU, the rates of blood transfusion and hemodialysis/continuous renal replacement therapy (CRRT) were more frequently applied in non-survivor group (p=0.03, OR:3.61, 95% CI:1.46-8.88, p<0.001, OR:4.1, 95% CI:2.22-7.75) Although APACHE II, SOFA and SAPS II scores at admission were not statistically different between each group, they were found to be higher in non-survivors on the day of VAP onset. When comparing survivor and non-survivors in terms of microorganisms causing VAP, only *Acinetobacter baumannii* isolates were found to be at a significantly higher rates in non-survivor group (p=0.01, OR:1.82, 95% CI:1.12-2.96). *Pseudomonas aeruginosa*

and *Klebsiella pneumoniae* infections were seen more commonly in non-survivor group, but the difference was not statistically significant. Variables that were found to be significant in univariate analysis were evaluated with Cox regression analysis to predict independent factors associated with the mortality of VAP. Only SOFA score on the day of VAP onset and *Acinetobacter baumannii* were found to be independently associated with 30-day mortality. Results of univariate and multivariate analysis are shown in Tables 1 and 2.

In the univariate analysis, rate of patients hospitalized with trauma was seen significantly higher in survivor group (p=0.009, OR:0.4, 95% CI:0.2-0.8). However, according to the Cox regression analysis, trauma was not found to be an independent factor for the survival of VAP patients (p=0.36, OR:0.74, 95% CI:0.39-1.40).

DISCUSSION

Although there are several guidelines for preventing ventilator-associated pneumonia, VAP continues to be one of the most common hospital-acquired infec-

tions seen in ICUs. VAP rates vary between each hospital and each ICU and it has been stated at different rates in the studies. While the incidence of VAP was 10.8/1000 ventilator days in a study conducted in Thailand, it was found as 50.87/1000 ventilator days in another study in Argentina^(14,15). In our country, it was found to be 16.1/1000 ventilator days in the study of Engin et al, 8.98/1000 ventilator days in the study of Erbay et al, and 23.3 in the study of Uslu et al.⁽¹⁶⁻¹⁸⁾. In our study, the VIP incidence was found to be 12.5/1000 ventilator days. Even in the same unit, VAP incidence may change over time. Therefore, it is important to follow the rates with surveillance regularly, and taking measures when there is an increase in VAP rates.

In the studies, Gram-negative bacteria have been reported as the most common isolates in VAP patients. Among these, the most common bacteria are *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*⁽¹⁹⁻²⁸⁾. In our study, the microorganisms caused VAP were similar to those studies regarding their order of frequency (Figure 1). *Acinetobacter baumannii* strains were isolated in half of our patients and *Pseudomonas aeruginosa* strains were isolated in 20% of the patients.

One of the most important issue in nosocomial infections is the increasing antibiotic resistance over the years. Increasing rates of resistance against carbapenems, which were used in the treatment of MDR microorganisms, cause serious difficulties in the treatment of these patients and increase mortality and morbidity^(29,30). In our study, carbapenem resistance was observed in 42.6% of the patients. *Acinetobacter* spp. and *Klebsiella pneumoniae* isolates have been reported to develop resistance to most antibiotics at increasing rates over the years^(22,27,31). In the "European Antimicrobial Resistance Surveillance Network" (EARS-Net) 2017 report, carbapenem resistance among *Klebsiella pneumoniae* isolates were reported as 64.7% in Greece, 29.7% in Italy and 22.5% in Romania⁽³²⁾. In Turkey, Candevir-Ulu et al. found carbapenem resistance to be 48% in the study conducted in ICUs in 2012⁽³³⁾. Akgül et al. reported that the carbapenem resistance against *K.pneumoniae* strains increased to 66.9% in 2014⁽³⁴⁾. In our study, although carbapenem resistance was

54.4% against *Acinetobacter* strains which were responsible for half of the VAP cases, it was higher (66.6%) against *Klebsiella pneumoniae* strains. As another finding, carbapenem resistance was found to be 40% in *E.coli* strains which were isolated in only 5 patients. With the widespread use of colistin for Gram-negative bacteria resistant to carbapenems, colistin resistance has also become a problem for these bacteria^(35,36). Koçak et al. found that 39.5% of 81 carbapenem-resistant *K.pneumoniae* isolates were also resistant to colistin⁽³⁷⁾. In our study, 4 (25%) of 16 carbapenem-resistant *Klebsiella pneumoniae* strains were also found to be resistant to colistin.

VAP has the highest mortality rates among nosocomial infections. In our study, the 30-day mortality rate was found to be higher (46.4%). VAP mortality rates have been reported in studies varying between 14-70%^(38,39). In a study conducted in China, the 30-day mortality rate was 42.8%, in a Brazilian study 35%, in another study overall mortality in VAP patients was found to be 32.4 percent^(40,6). There are several factors affecting mortality in the patients with VAP. In our study, survivor and non-survivors were compared to evaluate the risk factors affecting 30-day mortality. Although there are several studies showing that older age has negative impact on survival, in our study no statistical difference was observed between two groups in terms of their mean ages. When the underlying diseases were evaluated, the rate of malignancy was found to be significantly higher in the non-survivor group. In two studies conducted in Turkey, the history of coronary artery disease was found to be independently associated with mortality in VAP patients^(28,41). In a study conducted in Thailand, history of malignancy was found to be associated with mortality, similar to our study⁽¹⁹⁾. Immunosuppression predisposes patients to infections by impairing the host defense. But et al. found that corticosteroid use and history of malignancy were found to be higher in non-survivor group, similar to our study⁽²⁸⁾. Considering the effect of invasive procedures on mortality, blood transfusion and hemodialysis/CRRT were found to have a higher impact on mortality in the non-survivor group, but these variables lost their significance in multivariate analysis (Table 2).

When considering the univariate analysis, the proportion of patients with a history of trauma was found to be significantly higher in the survivor group (Table 1). Similarly, In a study performed in 2010, trauma and nontrauma groups were compared in VAP patients, and mortality was found to be lower in trauma patients⁽⁴²⁾. In our data, when comparing the patients with and without trauma, it was seen that patients hospitalized due to trauma were significantly younger, with relatively fewer underlying diseases and with lower scores both on admission and the day of VAP onset. The low mortality in trauma patients was attributed to these reasons.

APACHE II, SOFA and SAPS II scale scores at admission were not statistically different between each group, but when looking at scores at the time of VAP onset, it was seen that all scores of these scales were significantly higher in the non-survivor group (Table 1). Studies have shown that severity of illness is important for the prognosis after infections^(8,43,44). High scores in our study are compatible with the literature. According to the results of multivariate analysis, the SOFA scores at the time of VAP onset was independently associated with mortality. In a study carried out by Inchai et al, SOFA and SAPS II scores at the time of VAP onset were found to be associated with mortality⁽¹⁹⁾. In a study in China, SOFA scores were independently associated with mortality in VAP patients, and in another study, APACHE II scores at the time of VAP onset were found to be a poor indicator for prognosis^(40,45). In our study, only the SOFA scores at the time of VAP onset and *Acinetobacter baumannii* were found to be independent predictors of 30-day mortality in VAP patients (Table 2). *Acinetobacter baumannii* strains isolated in VAP patients have been shown in many studies to increase the mortality, and our results were compatible with the literature in this respect^(46,47).

The retrospective design and being a single-centre study are the major limitations of our study. Also our study did not investigate data about antimicrobial treatment, therefore we could not evaluate the effect of appropriateness of the antibiotherapy on mortality.

In conclusion, according to our results the most com-

mon cause of VAP was *Acinetobacter baumannii* isolated in half of the patients. Carbapenem resistance, one of the most important treatment challenges, was seen in more than half of *Acinetobacter baumannii* and *Klebsiella pneumoniae* isolates. Our study also has shown that VAP is associated with high mortality as well as high SOFA score on the day of VAP onset and *Acinetobacter baumannii* infections with poor outcome.

Ethics Committee Approval: Approval was obtained from Bakirkoy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (202-12 / 08.06.2020).

Conflict of Interest: none.

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Informed Consent: It is a retrospective study.

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